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Initiatives for Addressing Environmental Antimicrobial Resistance: Executive Summary

Inside Cover

This briefing summarizes knowledge gaps from a scientific white paper and discussion at the International Environmental Antimicrobial Resistance (AMR) Forum, a meeting hosted by the U.S. Centers for Disease Control and Prevention, the U.K. Science and Innovation Network, and the Wellcome Trust in April 2018. This scientific meeting gathered international technical experts, government officials, and key partners to outline the current knowledge of how resistant microbes and antimicrobials from multiple sources—human and animal waste, antimicrobial manufacturing, and the use of antimicrobials as pesticides—contributes to the presence of resistant microbes and antimicrobials in the environment and the potential impact of the affected environment on human health.

This briefing is supported by the scientific white paper *Initiatives for Addressing Environmental Antimicrobial Resistance: Current Situation and Challenges*, which was drafted by experts in this field and published alongside this executive summary in 2018, available online at [URL, tbd].

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Graphics in this report have been selected from illustrated minutes produced at the International Environmental AMR Forum by Sam Bradd, Drawing Change.

Key Messages

- AMR—when microbes (germs) develop the ability to defeat the drugs designed to combat them—is a threat to public health and a priority across the globe.
- Scientific evidence shows that antimicrobials and AMR can be present in the natural environment (waterways and soils), and AMR can spread in the environment. People exposed to antimicrobial-resistant pathogens like Methicillin-resistant *Staphylococcus aureus* (MRSA) and ESBL-producing bacteria in environmental waters are at increased risk of infection from this exposure.
- The full extent to which AMR and antimicrobials are found in the environment is not well understood, including how resistance spreads and the specific risks to human health. More research is needed to guide action, address knowledge gaps, and evaluate the potential risk antimicrobials and resistant microbes in the environment poses to human health and the broader environmental ecosystem.
    - Comprehensively addressing AMR requires a collaborative global approach using the One Health framework, which recognizes that the health of people is connected to the health of animals and the environment.
    - Effective action is reliant on more complete data, built from standardized indicators, methods, and targets in order to measure and monitor antimicrobial contamination and resistance in different environmental settings. Integrating environmental AMR assessment into public health surveillance, and sharing data across countries and sectors can help to provide a more comprehensive understanding on AMR in the environment.
- This executive summary and the supporting white paper, drafted by the assembled technical experts that participated in the International Environmental AMR Forum in 2018, outlines the current knowledge of how resistant microbes and antimicrobials from multiple sources—human and animal waste, antimicrobial manufacturing, and the use of antimicrobials as pesticides—may contribute to the presence of resistant microbes and antimicrobials in the environment and the potential impact of the affected environment on human health. The summaries also highlight the significant knowledge gaps and which measures are most important for mitigating risks.
    - This information is intended to act as a roadmap for stakeholders, including researchers, non-governmental organizations, and countries to work to fill knowledge gaps and improve national and international understanding on how to best evaluate and address AMR in the environment
- Despite knowledge gaps, there are a number of identified actions to address AMR in the environment and reduce the potential risks to human health. The environment is a key pillar of the One Health framework, and can be integrated into AMR global and national action plans. However, the threat of AMR in the environment varies greatly from country to country.
    - Stakeholders can work to understand their local situation, determine what action is needed, and move towards reducing identified risks to human health.
    - Stakeholders can consider integrating environmental AMR actions into existing global public health goals and efforts, such as Sustainable Development Goals; the Water, Sanitation and Hygiene Initiative; and the Global Health Security Agenda.
- As we improve local, national, and international understanding of AMR in the environment, and as we work collaboratively to enhance collective scientific understanding, we will be able to better identify best practices, recommendations, and actions that are most significant and can be considered for wider adoption.

Introduction

Antimicrobial resistance (AMR)—when microbes (germs) develop the ability to defeat the drugs designed to combat them—is a threat to public health and a priority across the globe. To date, AMR scientific research and actions by governments, civil society, and other stakeholders have prioritized focus on antimicrobial use (i.e., antibiotics, antifungals) and preventing spread of AMR in humans and animals. Recently, the focus has expanded to include the role of the natural environment, including in waterways and soils (collectively referenced as "environmental AMR").

Environmental AMR is a key facet of the AMR system. Scientific evidence shows that antimicrobials and AMR can be present in the natural environment (waterways and soils), and AMR can spread in the environment. People exposed to antimicrobial-resistant pathogens like MRSA and ESBL-producing bacteria in environmental waters are at increased risk of infection from this exposure.

The full extent to which AMR and antimicrobials are found in the environment is not well understood, including how resistance spreads and the specific risks to human health. More research is needed to guide action, address knowledge gaps, and evaluate the potential risk antimicrobials and resistant microbes in the environment poses to human health and the broader environmental ecosystem. However, it is known that antimicrobials and AMR can enter and contaminate the environment in several ways, including from:

- **Human and animal waste (i.e., feces):** Waste from people and animals can carry unmetabolized traces of previously-consumed antimicrobials, including those that are clinically important in human medicine. Waste can also carry antimicrobial-resistant microbes, and microbes with resistance mechanisms that can be shared among other microbes.
- **Manufacturing waste:** Release of active pharmaceutical ingredients (APIs) into the environment occurs when antimicrobials are manufactured.
- **Antimicrobial pesticides for crops:** Antimicrobials are used on crops to prevent or treat plant diseases throughout the world, some of these antimicrobials being the same or closely related to those used in human medicine.

When antimicrobials or resistant microbes are introduced into the environment, there is an opportunity for these elements to interact with other microbes, including those naturally occurring in these settings. This accelerates the development and spread of AMR through both the selective pressure applied by antimicrobials, and transmission (spread) of resistance genes between microbes.

Antimicrobial use can lead to AMR

Antimicrobials are vital tools for health, but their use can lead to an increase in AMR. AMR evolves through a process called natural selection, where organisms better adapted to their environment tend to survive and produce more offspring.

Antimicrobials apply selective pressure to microbes. This is because while some microbes will be killed by the antimicrobial, others resist the effects of the drugs and survive. The resistant microbes that survive pass their resistance trait to their offspring, creating more resistant microbes.

The more microbes are exposed to antimicrobials, the more likely it is that resistance traits are passed on and shared.

Modern trade and travel mean AMR can move easily across borders, with some types of AMR already widespread. To address AMR, a significant number of nations have national action plans (NAPs) in place. In

2016, the United Nations General Assembly held a high-level meeting to discuss the global challenge of AMR, prioritizing it through a political declaration. As a result, AMR remains a priority topic of global discussion.

Comprehensively addressing AMR requires a collaborative global approach using the One Health framework, which recognizes that the health of people is connected to the health of animals and the environment. Better understanding the risk environmental AMR poses to human health and how to effectively and efficiently mitigate this risk is a significant outstanding question that will require scientific research to inform responses. Despite these knowledge gaps, there are a number of identified near-term actions that can address AMR in the environment and reduce the potential risks to human health.

Human and Animal Waste

Human Waste

Waste and wastewater can contribute to the development and spread of AMR in the environment, negatively affecting human health. Antimicrobial residue and microbes, including resistant microbes, exit the human body through waste (feces, urine). Human waste and wastewater (used water from fixtures, like toilets) carrying antimicrobials and resistant microbes are often discharged to water bodies or land. In some cases, wastewater is reused. Studies have found detectable levels of resistant bacteria in surface waters (rivers, coastal waters) and people who were exposed to these microbes through interaction with contaminated water became ill.

Many countries have challenges in providing adequate sanitation—the ability to dispose of human waste safely and maintain hygienic conditions. In fact, globally, the majority of human waste is discharged directly into the environment without treatment. This includes open defecation and illegal dumping into waterways. Access to safe water, adequate sanitation, and proper hygiene education can reduce illness and death, including common illnesses, like diarrhea, as well as more severe cases and those caused by resistant microbes.

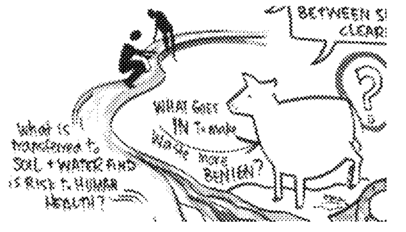
A major component of adequate sanitation is the use of wastewater treatment plants (WWTPs), which reduce contaminants, such as microbes, in wastewater before they are discharged. However, WWTPs can fail to remove the necessary contaminants before they are discharged into the environment when they are not maintained, have too much water volume (for example, during a storm), or are based on out-of-date technology. In addition, traditional WWTPs might not be sufficient at removing antimicrobials or AMR, particularly when levels of waste are high.

The risk of AMR in human waste is especially concerning when looking at treatment of wastewater from healthcare facilities like hospitals. Human waste from healthcare facilities can act as a significant source of antimicrobials, harmful microbes, and AMR because patients at these facilities have some of the most resistant infections and are commonly prescribed antimicrobials. The combination of antimicrobials and AMR in hospital waste streams allows resistant microbes to grow in facility plumbing systems, such as sinks, and even inside WWTPs. Healthcare facilities dispose and treat wastewater differently, often dependent on the type and location of the facility. This means that high levels of antimicrobial and AMR might not always be treated sufficiently to avoid environmental contamination.

More research is needed to better understand and mitigate the development of AMR from human waste. This includes waste water assessments for AMR to identify potential contamination and to evaluate WWTP effectiveness, especially when waste is delivered from high volume locations, and a better understanding of how to enhance hospital waste treatment. In some countries, there is also a need for wastewater treatment infrastructure, and, in other countries, innovative wastewater treatment technologies that address AMR. Additionally, integrating existing public health initiatives, such as the Water, Sanitation and Hygiene (WASH) efforts, will help in the effort to reduce environmental contamination and limit spread of AMR.

Animal Waste & Aquaculture

Using manure containing antimicrobials or resistant microbes as fertilizer could contribute to the development and spread of AMR through the environment. Animal waste is used as fertilizer on agricultural lands to help stimulate plant growth and maintain productive soils. However, similar to human waste, manure from food-producing animals that have been treated with antimicrobials can carry antimicrobial residue and resistant microbes, which could potentially contaminate the surrounding soil and nearby water sources. Further research is needed to fully determine the effects of animal waste contamination on human health and the broader environmental ecosystem. That said, people can become ill from contact with food animals or their manure.



Manure is usually processed prior to use as fertilizer, but the level of treatment is often dependent on setting and further research is still needed to understand how effective different treatments are at reducing antimicrobials and resistant microbes before application. Resistant microbes can also be introduced via biosolids—fertilizer material composed of treated human waste—but again, it is unclear how effective removal strategies are used before applying to crops. Research is also needed to better understand the aftereffects from trace contaminants of antimicrobial residue and resistant microbes in manure and biosolids entering the environment. However, recent studies suggest human exposure to these elements and environmental spread occurs.

Antimicrobials are also used worldwide in aquaculture, the farming of fish and seafood, to control disease. Aquaculture supplies more than half of all global seafood, and using antimicrobials could lead to AMR that affects human health. However, there are no confirmed human cases at this time. That said, estimates of antimicrobial use are difficult to compile, and there are limited efforts around collecting use data and other relevant data, such as sales of antimicrobials for aquaculture. Antimicrobials are also used in large quantities to support rearing ornamental fish (pets) and other aquatic species not meant for eating.

In aquaculture, antimicrobials are generally administered in feed or occasionally through bath treatments, potentially contaminating the local aquatic environment with antimicrobial residue and microbes through fish waste matter and discharge of dissolved antimicrobials into the water column. This form of antimicrobial use, if not practiced sustainably, could drive resistance development.

Contamination of the environment with animal waste containing antimicrobial residue could be reduced through appropriate use of antimicrobials in animal agriculture. The development of alternative disease control methods, such as vaccination-based strategies, could reduce reliance on use of antimicrobials. In addition, establishing better early warning systems for the emergence of disease and improving the quality of the rearing environment can help reduce the need for antimicrobials. These actions will help reduce the level of antimicrobial residue in waste to limit environmental contamination, and also support goals to improve stewardship of antimicrobials in animals. However, in some cases, work is needed to develop these methods and support their implementation in such a way that both animal welfare and business sustainability is maintained.

Addressing Knowledge Gaps

Scientific review suggests that the following actions could improve understanding and guide action:

- Conduct studies to understand the drivers of AMR in recreational and drinking water, including identifying sources of resistant pathogens (human or animal), selective pressures driving amplification (e.g., co-selecting agents like heavy metals), and identifying mechanisms for amplification and transmission (e.g., horizontal gene transfer)
- Improve sanitation globally by conducting research to identify efficient and affordable wastewater processing methods that are easily implemented where processing doesn't currently exist or as enhancements to existing processing where levels of AMR are high
- Understand the risk of antimicrobial-resistant microbes in environmental waters by conducting studies to assess where microbes are present and how much is there
- Conduct evaluation studies of potential environmental contamination between waste influent and waste processing (e.g., WWTP) to help to determine if on-site pre-treatment of wastewater is needed
- Conduct studies to evaluate the presence of antimicrobial-resistant microbes and antimicrobials in post-processing waste streams to measure the effectiveness of treatment processes in areas where AMR and antimicrobial levels in wastewater are likely to be high, such as hospitals, sewage systems, and farms
- Investigate and identify factors that improve wastewater treatment efficiencies and those factors that contribute to inefficiencies and failures (e.g., ineffective processing method or infrastructure failures)
- Conduct research to identify and develop alternatives to antimicrobials to prevent and control disease in aquaculture

Manufacturing Waste

The manufacturing of antimicrobials by pharmaceutical companies can contribute to the development of environmental AMR. Effluent (waste discharged into a water body) from the manufacturing process can include antimicrobials, resistant microbes, and active pharmaceutical ingredients (APIs) even after treatment, and is frequently discharged into the local environment. The levels of antimicrobials and APIs can be very high, with evidence to show that there is an increase in levels of resistance in the local waters. Studies have found APIs in rivers, treated or untreated manufacturing wastewater, and sediment downstream of industrial wastewater treatment plants. The full extent to which manufacturing waste directly affects human health is not well understood; however, this waste is an important and often neglected source of antimicrobials and of AMR contamination in the environment, specifically in countries where antimicrobials are manufactured.

Eliminating or significantly reducing antimicrobial residue and other contaminants in manufacturing waste is a critical step in mitigating environmental AMR. While some manufacturers have set voluntary limits, there are no national or global standards to limit the level of contamination in manufacturing effluent because a "safe discharge limit" has not been established. Companies often have an environmental risk-management strategy that aims to minimize impact of antimicrobials discharged from manufacturing processes. However, data on the amount of APIs released in wastewater discharges is not publically available, making it difficult to understand the full scope of the problem and generate a risk assessment. At the same time, methods to analyze APIs in discharged manufacturing wastes and in aquatic environments exist, but an internationally recognized standard method is needed to compare results from different factories.

Addressing these data and methodology gaps would help researchers identify risk to human health and guide viable and effective actions to mitigate this risk. Fostering agreement on a discharge limit for effluents leaving manufacturing sites (i.e., not zero, but sufficiently low to be protective while still being technically achievable) and reporting levels could significantly reduce environmental contamination. A subset of the industry has already provided leadership on best practices for responsible waste management[i], with several voluntary industry initiatives for responsible manufacturing and sourcing already underway. More action and collaboration is needed to better understand and manage manufacturing waste.

Addressing Knowledge Gaps

Scientific review suggests that the following actions could improve understanding and guide action:

- Develop and validate standardized monitoring methods for testing antimicrobial agent runoff from the manufacturing process
- Conduct pilot studies to evaluate the feasibility and cost of limiting discharge to discharge targets (i.e., discharge limits) proposed by scientific experts
- Identify and evaluate incentives (e.g., green procurement) to reduce pharmaceutical manufacturing contaminants in a timely and effective way
- Identify or develop strategies to limit environmental contamination in countries where antimicrobial manufacturing occurs. Work with industry partners, such as the AMR Industry Alliance, to evaluate strategies

Antimicrobial Pesticides for Crops

Antimicrobials are commonly applied across the globe as pesticides to manage crop disease. These diseases can be difficult to control and extremely damaging if left untreated. However, applying antimicrobials can accelerate the development and spread of AMR in the environment by contaminating the surrounding soil and water. While further research is needed to determine the effects of antimicrobial-based pesticides on human health and the broader environmental ecosystem, there are specific concerns for human health where antimicrobial pesticides are the same as, or closely related to, antimicrobials used in human medicine.

There is evidence of microbes developing resistance to these pesticides, and, in some cases, these microbes also cause human infections. For example, triazole is the most widely used fungicide on crops, but is also important human medicine to prevent or treat fungal infections. Already some human triazole medications are no longer effective following the development of resistant fungi such as *Aspergillus fumigatus*. There is also an increased risk to human health through the exposure of workers who apply antimicrobial pesticides. In some countries, pesticide applicators wear personal protective equipment, but there is limited knowledge on how effective the equipment is at minimizing exposure to the antimicrobial pesticide. Further research is needed to determine the effects of pesticides on human health and the broader environmental ecosystem.

Comprehensive information is not collected on which antimicrobials are being used, where, and at what levels. Collecting, monitoring, and analyzing this data would greatly support the identification of possible links between antimicrobial pesticides and the emergence of resistant microbes that cause human infections. This data would also guide research to determine the impact of antimicrobial pesticides on human health and the surrounding environment, including soil, water, plants and animals. Additionally, there are no established science-based principles in national AMR action plans around antimicrobial pesticide use. Support is needed to identify and develop alternative disease prevention and treatment strategies, such as modeling to predict high-risk periods for crop disease. These actions could help improve antimicrobial use, and minimize exposure to humans and the surrounding environment.

Addressing Knowledge Gaps

Scientific review suggests that the following actions could improve understanding and guide action:

- Conduct research to determine the impact of antimicrobial pesticide exposure on the human, plant, and animal microbiomes
- Identify and promote best practices for applying antimicrobials as pesticides to minimize exposure to humans, animals, and the surrounding environment
- Establish greater global transparency of antimicrobial use as pesticides by collecting information like the amount of antimicrobial used on crops each year
- Share data between countries on the relative efficacy of antimicrobials as pesticides and potential alternatives, so that antimicrobials used in human medicine are only considered when there is evidence of efficacy and no alternatives are available
- Conduct studies to develop alternatives to antimicrobials to prevent or treat crop disease and identify strategies to ensure that alternative treatments are available to growers
- Identify and develop appropriate and reproducible methods to monitor the crop field and surrounding environment to determine if there are increases in antimicrobial resistance when medically important antimicrobials are used and when co-selection is a concern
- Consider updating national AMR action plans to include antimicrobial stewardship principles for using antimicrobials as pesticides with actions that are based upon country-specific practices

Conclusion

Environmental contamination by antimicrobials and resistant microbes presents a significant challenge to the global community in the effort to tackle AMR. Scientific evidence shows that antimicrobials and AMR are present in the environment, AMR spreads in the environment, and this form of environmental contamination can affect human health. More research is needed to guide action, address knowledge gaps, and evaluate the potential risk antimicrobials and resistant microbes in the environment poses to human health and the broader environmental ecosystem.

Effective action is reliant on more complete data, built from standardized indicators, methods, and targets in order to measure and monitor antimicrobial contamination and resistance in different environmental settings. Integrating environmental AMR assessment into public health surveillance, and sharing data across countries and sectors can help to provide a more comprehensive understanding on AMR in the environment.

This executive summary and the supporting white paper, drafted by the assembled technical experts that participated in the International Environmental AMR Forum in 2018, highlight data identifying the potential for the environment to be a source of AMR pathogens that can affect human health. They also highlight the significant knowledge gaps and which measures are most important for mitigating risks. This information is intended to act as a roadmap for stakeholders, including researchers, non-governmental organizations, and countries to work to fill knowledge gaps and improve national and international understanding on how to best evaluate and address AMR in the environment.

Despite knowledge gaps, there are a number of identified actions to address AMR in the environment and reduce the potential risks to human health. The environment is a key pillar of the One Health framework, and can be integrated into AMR global and national action plans. However, the threat of AMR in the environment varies greatly from country to country. Stakeholders can work to understand their local situation, determine what action is needed, and move towards reducing identified risks to human health. Consider integrating environmental AMR actions into existing global public health goals and efforts, such as Sustainable Development Goals; the Water, Sanitation and Hygiene Initiative; and the Global Health Security Agenda. As we improve local, national, and international understanding of AMR in the environment, and as we work collaboratively to enhance collective scientific understanding, we will be able to better identify best practices, recommendations, and actions that are most significant and can be considered for wider adoption.

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[i] Ibid.